REMARKS

Formal Matters

Applicants thank the Examiner for withdrawing the rejection of claims 13-16, 19-21, and 32, as failing to comply with the written description requirement. *See* Office Action at ¶ 2. Applicants believe that paragraph four was inadvertently left in the text of the present Office Action. The text of paragraph four relates to the Examiner's support for the earlier rejection of claims 1, 4, 6-21, and 33, as failing to comply with the enablement requirement and is identical to the text of paragraph six in the Office Action mailed February 4, 2004. However, as the preceding paragraph of the present Office Action states, the "rejection of claims 1, 4, 6-21, and 33 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement is withdrawn." Office Action at ¶ 3. Applicants request that the Examiner confirm the withdrawal of the enablement rejection. Applicants also note that the Examiner did not reinstate the rejection of claims 1, 4, and 6-33 as being indefinite and therefore this rejection is deemed withdrawn. *See* Office Action at ¶ 13.

Applicants have added new claims 34-42, which correspond to previously canceled claims 22-27 and 30-32, as discussed in the "New Claims" section below.

Claims 1, 4, 6, 9-16, 19-21, and 33-42 are now pending in this application.

Finality of the Office Action

The Office Action dated July 29, 2004, has improperly been made final. Accordingly, Applicants respectfully request that the finality be withdrawn.

The Examiner introduced a new ground of rejection that was not necessitated by Applicant's amendment of the claims. Section 706.07(a) of the MPEP provides that an Office Action containing such a rejection should not be made final. Six new obviousness rejections of pending claims 1, 4, 6, 9-16, 19-21, and 33 were introduced for the first time in the present Office Action. In the Amendment filed May 4, 2004, Applicants merely narrowed the scope of the claimed invention. If the claims *after* the amendments are allegedly obvious, then they would have been allegedly obvious *before* those amendments. The present Office Action, however, recites for the first time any rejection of claims 1, 4, 6, 9-16, 19-21, and 33 under 35 U.S.C. § 103.

The new obviousness rejections parallel the obviousness rejections of claims 22-32, which were presented in the previous Office Action, dated February 4, 2004. Application of these rejections to the pending claims in the present Office Action is contrary to PTO policy as set forth in the MPEP.:

> To bring the prosecution to as speedy conclusion as possible and at the same time to deal justly by both the applicant and the public, the invention should be thoroughly searched in the first action and *the references fully applied*; and in reply to this action the applicant should amend with a view to avoiding all the grounds of rejection and objection.

MPEP § 706.07 (emphasis added). By failing to fully apply *Potts*, *Schlom*, *Gristina*, *Seger*, and *Sato* in the first Office Action, the Examiner has denied Applicants

the full opportunity to establish the patentability of the claimed invention over these documents. Accordingly, the finality of the new rejections should be withdrawn.

New Claims

Applicants have added new claims 34-42, which correspond to previously canceled claims 22-27 and 30-32. Applicants canceled these claims to expedite prosecution by separately pursuing claims that were not rejected under 35 U.S.C. § 103 (claims 1, 4, 6, 9-16, 19-21, and 33). However, because the Examiner in the present Office Action has belatedly rejected claims 1, 4, 6, 9-16, 19-21, and 33 as allegedly being obvious, Applicants have reinstated the previously canceled claims as new claims 34-42. Applicants respond to the rejections of previously canceled claims 22-32 in detail below. Further, Applicants respond to the obviousness rejections of the currently pending claims in the section "Rejections under 35 U.S.C. § 103(a)."

The Examiner rejected claim 22 [new claim 34] because it is "unclear if the requirement of the claim is that the patient be actually exhibiting impaired consciousness at the time of treatment." 2/4/04 Office Action at ¶ 4. Applicants respectfully traverse this rejection. However, Applicants removed the phrase "associated with impaired consciousness" from previously canceled claim 22 and further revised the preamble at the suggestion of the Examiner to recite "A method for treating hypercalcemic crisis associated with malignant tumor." Applicants respectfully submit that new claim 34 is definite.

The Examiner also rejected claim 28 for allegedly being unclear as to how it limits the scope of independent claims 22 or 25. 2/4/04 Office Action at ¶ 4. Applicants respectfully traverse, however Applicants did not add previously canceled claim 28 as a new claim.

The Examiner also rejected claim 27, as being "vague and indefinite in the recitation of #23-57-137-1 as the only means of identifying the monoclonal antibody on which the claims depend." *Id.* Applicants respectfully traverse, however have amended previously canceled claim 27 to recite the Deposit Accession Number. Applicants respectfully submit that new claim 39 is definite.

The Examiner also rejected claims 1, 4, and 6-33 because the Specification "does not reasonably provide enablement for methods of treating hypercalcemic crises having increased calcium levels from other causes than elevated levels of PTHrP." 2/4/04 Office Action at ¶ 7. Further, the Examiner cites Sato (Journal of Bone and Mineral Research, 1993, vol. 8, pp. 849-860), which allegedly demonstrates that "immunization of a hypercalcemic mouse bearing a transplanted parathyroid carcinoma which secretes PTH rather than PTH-rP, did not effect the blood calcium concentration." *Id.* In their response dated May 4, 2004, Applicants amended the preamble of claim 1 and 15 to read "A method for treating a patient suffering from or susceptible to hypercalcemic crisis associated with malignant tumor." Applicants also cancelled claims 8 and 18, which did not further limit the claims as amended. The Examiner withdrew this enablement rejection of claims 1, 4, 6-21 and 33 in light of this

amendment and response. Applicants therefore respectfully submit that previously canceled claims 22-27 and 30-32 [new claims 34-42] are also enabled.

The Examiner also alleged that the values described in the Specification at page 6, lines 6-22 "do not provide support for the broader claim [previously canceled claim 22; new claim 34] drawn to 'decreasing a blood calcium level to effectively treat the patient'." 2/4/04 Office Action at ¶ 5. Applicants respectfully traverse. A person skilled in the art at the time the application was filed would have recognized that the inventors were in possession of the invention as claimed in view of the disclosure of the application as a whole. For instance, the Specification states "[p]referably, the therapeutic agent for hypercalcemic crisis according to the present invention can decrease the calcium level rapidly after the administration of the agent." Specification, page 6, last paragraph (emphasis added). In addition, Example 1 of the Specification details a pharmacological test on a model animal with hypercalcemic crisis, and demonstrates that administration of an anti-PTHrP antibody rapidly reduces blood calcium level. *See* Specification at pages 24-28.

In light of the information detailed in the Specification, one of skill in the art would know when the reduction in blood calcium level was effective in treating a patient. Hypercalcemic crisis is a disorder well known in the art and its symptoms are defined. The symptomology of the disease and other general information occupy distinct entries in the prior art and is described in the Specification at, for instance, page 2, lines 3-6. One of ordinary skill in the art would therefore be able to decrease a blood calcium level and determine when such a decrease was effective, especially given the teachings of

the Specification and the prior art. Applicants therefore respectfully submit that new claim 34 meets the written description requirement.

The Examiner also alleges that the specification makes no mention of using the instant methods as a 'fall back' in the case that the hypercalcemia is resistant to calcitonin, furosemide, etc." 2/4/04 Office Action at ¶ 5. Applicants respectfully traverse. A person skilled in the art at the time the application was filed would have recognized that the inventors were in possession of the invention as claimed in view of the disclosure of the application as a whole. For instance, the Specification states that drugs such as calcitonin, steroid, a biphosphonate, etc. "have such disadvantages that therapeutic effects may be depressed when successively administered, that severe adverse side effects may be produced, and that the development of pharmacological effects may be delayed." Specification at page 3, lines 13-18. Further, the Specification describes the resistance of hypercalcemic crisis to a prior art calcitonin preparation, which was unable to maintain decreased blood levels of calcium and to increase body weight to normal levels. *See* Specification, Example 1, pages 24-28; Figures 1-6. One of ordinary skill in the art would therefore be able to determine if a prior art composition was not effective in treating hypercalcemic crisis, especially given the teachings of the Specification. Although Applicants traverse this rejection, Applicants have deleted the phrase "drug-resistant" from previously canceled claims 22 and 23. In light of this amendment and arguments detailed above, Applicants respectfully submit that new claim 34 meets the written description requirement.

Rejections under 35 U.S.C. § 103(a)

In the present Office Action, the Examiner makes several obviousness rejections. As shown in the bracketed text below, Applicants will also address the similar obviousness rejections of previously canceled claims 22-32 [new claims 34-42] presented in the Office Action mailed February 4, 2004.

> 1. Claims 1, 4, 9, 10, 12, 13-15, 19, 20, and 33 [34-38 and 40-42] are rejected as being obvious over *Seger* (U.S. Patent No. 5,494,806) in view of *Potts* (Diseases of the Parathyroid Gland and other Hyper- and Hypocalcemic Disorders, In: Harrison's Principles of Internal Medicine, 12th Edition, pages 1902-1915) and *Schlom* (In: Molecular Foundations of Oncology, Sameule Broader, Ed., 1991, pages 95-134). 7/29/04 Office Action at 3. [2/4/04 Office Action at 6.]
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> 2. Claims 1, 4, 9-15, 19-21, and 33 [34-38 and 40-43] are rejected as being obvious over *Seger* and *Potts* and *Schlom* and further in view of *Gristina* (U.S. Patent No. 5,681,565). 7/29/04 Office Action at 5. [2/4/04 Office Action at 9.]
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> 3. Claims 1, 6, 9, 10, 13, 16, 19, 20, and 33 [34-35 and 39-41] are rejected as being obvious over the abstract of *Sato* (WO 98/13388) in view of *Potts.* 7/29/04 Office Action at 6. [2/4/04 Office Action at 10.]
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> 4. Claims 1, 4, 6, 9, 10, 12, 13-16, 19, 20, and 33 [34-41] are also rejected as being obvious over *Sato* and *Potts* and further in view of *Schlom.* 7/29/04 Office Action at 7. [2/4/04 Office Action at 12.]
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> 5. Claims 1, 4, 6, 9, 10, 12, 13-16, 19, 20, and 33 [34-41] are also rejected as being obvious over *Sato* and *Potts* and *Schlom* and further in view of *Gristina.* 7/29/04 Office Action at 8. [2/4/04 Office Action at 12-13.]

The Examiner cites *Seger* for teaching a method of treating hypercalcemia comprising the administration of antagonists of PTHrP. Office Action at 3. The Examiner states that *Sato* teaches the use of humanized #23-57-137-1 monoclonal antibody to treat hypercalcemia and other disorders caused by cancer. Office Action at 6. Finally, the Examiner cites *Potts* as teaching that the humoral mediator of malignancy associated with hypercalcemia is PTHrP. *Id.* Applicants respectfully traverse these rejections.

Applicants submit that none of the references cited by the Examiner teach or suggest the use of any agents to treat hypercalcemic crisis. While these references discuss the treatment of hypercalcemia, there are many shortcomings associated with the use of prior art treatments for hypercalcemia in the treatment of hypercalcemic crisis. It was therefore surprising that humanized PTHrP antibodies of the invention were able to effectively treat hypercalcemic crisis, by maintaining a decrease in plasma calcium concentration, for instance. Applicants provide a more detailed explanation of the difficulties in the treatment of hypercalcemic crisis, as evidenced in the specification, prior art, and references provided by the Examiner. Further, Applicants have enclosed the declaration of Toshiaki Tsunenari, Hidemi Saito, and Etsuro Onuma, detailing the nonobvious properties of the methods of the invention.

The specification illustrates that it was well recognized that traditional treatments for hypercalcemia did not effectively treat hypercalcemic crisis. The need for drugs having higher therapeutic effects and fewer side effects exists because traditional hypercalcemia treatments "have such disadvantages that therapeutic effects may be depressed when successively administered, that severe adverse side effects may be produced, and that the development of pharmacological effects may be delayed." Specification, page 3, lines 10-19; *see also* Tsunenari *et al.* declaration, ¶ 3. While these agents may be effective in treating hypercalcemia, the problems associated with their use in treating hypercalcemic crisis are many. The *Potts* reference cited by the Examiner also acknowledges the shortcomings of hypercalcemia agents for the treatment of hypercalcemic crisis. *See also* Tsunenari *et al.* declaration, ¶ 3. For

instance, *Potts* states that "[i]ntravenous phosphate is one of the most dramatically effective treatments available for severe hypercalemia but is toxic and even dangerous so that it is used rarely." *Potts*, page 1914, left column. Further, "escape from drug [calcitonin] action occurs in patients and animals invariably after 12 to 24 h of high-dose continuous therapy or after several days of repeated therapy with calcitonin." *Potts*, page 1913, right column, fourth paragraph.

The lack of efficacy of typical hypercalcemia treatments is demonstrated in Example 1 of the Specification as well as the Tsunenari *et al.* declaration. Using a hypercalcemic crisis model animal (a human tumor-transplanted nude mouse), a humanized antibody against PTHrP as well as a prior art calcitonin preparation were examined for their therapeutic efficacy. *See* Specification, Example 1, pages 24-28. Calcium levels were basically unchanged in rats treated with Elcitonin (a calcitonin preparation) and untreated rats after 24 hours. Specification, page 27; figures 3 and 5. The humanized PTHrP antibody of the invention, however, is able to reduce blood calcium level by 1 mmol/L after 24 hours of treatment. *Id.* Further, as demonstrated by Figures 4 and 6, the humanized PTHrP antibody of the invention is able to increase body weight, whereas Elicitonin and control are ineffective.

In a similar experiment, hypercalcemic crisis model rats were treated with humanized anti-PTHrP antibody (CAL), calcitonin (eCT), or biophosphonate (ALN). *See* Tsunenari *et al.* declaration ¶ 5. The results demonstrated that only the anti-PTHrP antibody was effective at rapidly and persistently lowering calcium levels. *See* Tsunenari *et al.* declaration ¶ 6 and attached experimental data. The ALN did not act

rapidly, and provided an effect too slow to treat hypercalcemic crisis, whereas calcitonin acted rapidly, but produced only a transient effect. *Id.* Thus, administration of compositions of the present invention are able to continuously and effectively suppress calcium levels when calcium rapidly increases to severe levels during hypercalcemic crisis, and can be rapidly effective, yielding results in as little as four hours.

The *Sato*, *Seger*, and *Potts* references provided by the Examiner discuss the use of various agents in the treatment of hypercalcemia. However, these references provide no reasonable expectation that the agents would be similarly effective in the treatment of hypercalcemic crisis. Data provided in the specification and the enclosed declaration demonstrate that prior art agents are unable to effectively treat hypercalcemic crisis. Yet surprisingly the humanized antibody of the present invention is able to rapidly decrease and maintain calcium level, while at the same time increasing body weight to normal levels.

In addition to *Sato*, *Seger*, and *Potts*, the Examiner cites *Schlom* (teaching the use of antibody fragments for maximum penetration into the tumor vasculature), and *Gristina* (teaching PEG as an antibody carrier) as support for the obviousness rejection. *Schlom* and *Gristina*, however, do not cure the defects described above, as they do not teach or suggest the use of humanized PTHrP antibodies to treat hypercalcemic crisis. Based upon the difficulties described above and the Applicants unexpected success, Applicants submit that the present invention is nonobvious and respectfully request that the obviousness rejections be withdrawn.

Obviousness-Type Double Patenting Rejections

The Examiner provisionally rejected claims 1, 4, 6-16, 19-21 and 33 [new claims 34-40] under the doctrine of obviousness-type double patenting, stating that these claims are not patentably distinct over claims 126-136 and 138 of copending Application No. 09/269,332 in view of *Potts* and *Schlom*. 7/29/04 Office Action at ¶ 11 [2/4/04 Office Action at ¶ 13]. Further, the Examiner provisionally rejected claims 1, 4, 6-16, 19-21 and 33 [new claims 34-42] under the doctrine of obviousness-type double patenting, stating that the claims are not patentably distinct over claims 126-136 and 138 of copending Application No. 09/559,344 and *Potts* and *Schlom* and in further view of *Gristina*. 7/29/04 Office Action at ¶ 14 [2/4/04 Office Action at ¶ 14].

Applicants will consider filing a terminal disclaimer to overcome these rejections once patentable subject matter has been indicated in this case. Until then, Applicants request that the Examiner hold the rejections in abeyance.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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